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Optimal Net Benefit for Spina Bifida Screening

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SUMMARY

Open spina bifida is one of the most common neural tube defects and one of the most serious that originates early in pregnancy. There is no cure. One way to address this problem is through early detection and prevention.

The objective of this research is to identify risk cutoff values in maternal serum alpha-fetoprotein (MSAFP) screening that maximize the economic benefits to society. The MSAFP is a blood test where a risk cutoff value is selected. An individual testing at or above this value is considered at increased risk of having a fetus with spina bifida. A net benefit approach is used to identify several risk cutoff values at different incidence rates. The net benefit approach consists of several steps. First, this approach uses a formula that assumed benefits and costs to prenatal screening for spina bifida, with the difference being the net benefit. There are three rates that influence this formula: incidence rate, detection rate and false positive rate. Next, this method uses simulated data of detection and false positive rates that correspond to different risk cutoff values. The results from the simulation are inserted into the net benefit formula, which produces the net benefit at each risk cutoff value and incidence rate. The net benefit approach is the tool used to evaluate if current screening is being optimized. This approach does not attempt to pass judgment on the life of an individual. This is one approach to address prenatal screening for spina bifida.

The results show that there are different optimal risk cutoff values, depending on the incidence rate selected. If clinics use accurate incidence rates, rates that directly reflect the population they are screening, screening can be optimized. The

optimal risk cutoff value(s) for that specific incidence rate can be used. This benefits the patient, the medical community and society.

The net benefit approach is a useful tool for screening for spina bifida. The sensitivities of the individual must continue to be taken into consideration.

Background

Birth defects are the leading cause of infant mortality in the United States. Among birth defects, neural tube defects are some of the most serious malformations that originate early in pregnancy. Open spina bifida is one of the most common neural tube defects. This disorder occurs when the spinal cord does not develop properly and the skin cannot form and cover the spinal cord and vertebrae. Individuals with spina bifida require extensive medical treatment throughout their lives. Surgical intervention, therapy, special education and institutional care are common. Disabilities can include weakness or paralysis of the legs, urinary and fecal incontinence, hydrocephaly and mental retardation (Wald and Cuckle, 1984).

Spina bifida affects not only the individual, but families and society as well. Medical care costs are burdensome to the family. In addition, time spent traveling to and from appointments and the psychological and emotional effects are intangible costs borne by the families that deal with this every day. The burden to society can be calculated through the loss of potential earnings for individuals with spina bifida. The national incidence for spina bifida (reported by the CDC in 1995) is 4.6 per 10,000 live births or 1 per 2,174 live births. There are over four million births in the United States every year. There were 4,064,948 births in 2000 (NVSS, 2001). This incidence implies approximately 1,870 cases of spina bifida. The CDC also reports that the average lifetime cost estimated for a person with spina bifida is $532,000. The cost to society is approximately $1 billion per year.

There is no cure for spina bifida. However, one action that can be taken is prevention. In this case, prevention can be achieved through the utilization of diagnostic and screening tests. Diagnostic tests can identify cases of spina bifida with near perfect accuracy. Once a case of spina bifida is identified, action may be taken to terminate the pregnancy. Prenatal screening tests are used to identify the risk of potential birth defects and give families time to prepare and make decisions that may affect the outcome of pregnancy. However, diagnostic and screening tests involve risks and specific considerations that must be taken into account, as will be discussed in this paper.

Amniocentesis is the diagnostic test used to positively identify a fetus with open spina bifida. This test is a medical procedure performed during pregnancy to help determine the health of a fetus. It involves the withdrawal of a small amount of amniotic fluid that surrounds the fetus in the mother's uterus. With this procedure, spina bifida is 1 of more than 150 serious birth disorders that can be diagnosed. Prior to the 1980s, it was the main tool used in screening for neural tube defects. However, with improvements in the accuracy of ultrasound (one type of screening test), the screening protocol has changed. Amniocentesis is now primarily used if the screening tests show positive results and the pregnant woman agrees to accept certain risks associated with this procedure.

The most significant risk is that amniocentesis may cause the affected or unaffected fetus to spontaneously abort. If the amniocentesis were administered to every pregnant woman in the United States, based on the rate of spontaneous abortion with this procedure, this would result in the loss of approximately 20,325 fetuses (4,064,948 births x 0.005% (Beazoglou, et al., 1998)). This would also result in the detection of 1,870 cases of spina bifida (4,064,948 births x 1/2174 (incidence rate)).

In addition to posing a risk to the fetus, amniocentesis is the most costly (compared to screening tests) to administer. The average cost is $1200 (Vintzileos, et al., 1998). The cost of administering this diagnostic test to every pregnant woman would be approximately $4.9 billion per year (4,064,948 births x $1200). Based on these two factors, risk of fetal loss and cost, it is clear that amniocentesis cannot be administered to every pregnant woman. Therefore, it is important to optimize the use of screening to avoid unnecessary fetal losses and to reduce economic costs.

The utilization of screening tests is a preliminary method for spina bifida. Maternal serum alpha-fetoprotein (MSAFP) and routine ultrasonography are the specific tests used to detect cases of open spina bifida. The MSAFP is a blood test administered between the 16th and 18th weeks of pregnancy, the optimum gestational age to conduct MSAFP screening as determined by the First U.K. Collaborative Study (Knight and Palomaki, 1992). A cutoff value is selected for this test, with above-average levels indicating an increased risk of spina bifida.

The ultrasound is an important supplement to MSAFP screening. Although historically the ultrasound test was not very accurate, the detection rate has increased to more than 80% (Vintzileos, et al., 1998) over the past two decades. Ultrasound helps reduce the proportion of unaffected pregnancies regarded as having elevated MSAFP levels. It does this by revising the estimate of gestational age in women who appear to have elevated levels due to the underestimation of the gestational age. It is important to note a distinction with regard to ultrasound screening. Genetic ultrasound screening, the most precise method of ultrasound screening, has higher detection rates than routine ultrasounds. However, this screening procedure is not available in every area in the United States.

While neither the MSAFP nor the ultrasound screening tests pose risks to the fetus, there are differences between the two methods in both accuracy and cost. The ultrasound has been shown to have a high detection rate, yet is more expensive than the MSAFP screening test ($300 vs. $20; Vintzileos, et al., 1998 and Beazoglou, et al., 1998, respectively). The accuracy of the MSAFP screening test depends on the risk cutoff value selected. The risk cutoff value determines how accurate the test will be (detection rate and false positive rate). As in the case of the amniocentesis, it is not economically feasible to administer the ultrasound to every pregnant woman. The cost of administering ultrasound screening for every pregnant woman would amount to approximately $1.22 billion per year (4,064,948 births x $300 (Vintzileos, et al., 1998)). Therefore, MSAFP screening, the least expensive test in this process, is the recommended first step in screening for spina bifida.

Screening tests do not provide a clear-cut distinction between affected and unaffected fetuses. This is an extremely important concern because there is an overlap between the MSAFP levels found in affected and unaffected pregnancies. As stated earlier, in order to detect cases of open spina bifida through MSAFP screening, one risk cutoff value is selected. Any results that are at or above that risk cutoff value are considered to be positive. That is, those fetuses are identified as more likely to be affected. Similarly, any results below the selected risk cutoff value are considered negative, and less likely to be affected. There is no specific MSAFP cutoff value that completely separates the unaffected from the affected pregnancies.

As with any non-diagnostic screening test, there is a range of trade-offs associated with the risk cutoff value chosen. The risk cutoff value selected inherently determines and influences the detection rate and false positive rate. Appendix 1 demonstrates the sensitivity of choosing various risk cutoff values. The cutoff value that is chosen varies across clinical labs. In the United States, most labs use 2.0 or 2.5 MOM (multiples of the median) as the cutoff value (Knight and Palomaki, 1992).

The MSAFP screening test is not 100% accurate and affected cases may not be detected. Similarly, unaffected cases may be incorrectly identified as affected. Figures 1 and 2 in Appendix 1 each illustrate two distributions: unaffected and affected. There are four areas in each distribution influenced by the risk cutoff value: true negative, false negative, true positive and false positive. True negative represents the pregnancies that have unaffected fetuses and are classified as unaffected. False negative represents the pregnancies that have affected fetuses, but that are erroneously classified as unaffected. True positive represents the pregnancies that have affected fetuses and are classified as affected. False positive represents the pregnancies that have unaffected fetuses, but that are erroneously classified as affected. Figure 1 shows a selected risk cutoff value of 2.0 MOM. The curve to the left (U) represents the unaffected fetuses. The curve to the right (A) represents the affected fetuses. It is important to note that these two distributions are not to scale. The curve to the left (U) represents the over 4 million births per year. The curve to the right (A) represents the 1,870 cases of spina bifida (based on the 1/2174 incidence rate). The distribution for the unaffected cases that are erroneously classified as positive for spina bifida is represented by all of the cases to the right of that line.

Therefore, the area ABC represents cases that are considered affected, when in fact they are unaffected. These represent the false positive cases. The distribution for affected cases, at the same 2.0 MOM level, that are erroneously classified as unaffected for spina bifida is represented by all of the cases to the left of that line. Therefore, the area ABD represents cases that are considered unaffected, when in fact they are affected. These represent the false negative cases.

Figure 2 can also be used to illustrate the proportional change in the four areas if a higher risk cutoff value of 3.0 MOM is selected. Once again, the curve to the left (U) represents the unaffected fetuses and the curve to the right (A) represents the affected fetuses. When the 3.0 MOM value is selected as the risk cutoff value, all cases to the right of that vertical line are considered affected. Similarly, all cases to the left of the vertical line are considered unaffected. Therefore, the area ABC represents cases that are considered affected, when in fact they are unaffected, the false positive cases. Similarly, when the 3.0 MOM level is selected as the risk cutoff value, all cases to the left of the vertical line are considered unaffected. Therefore, the area ABD represents cases that are considered unaffected, when in fact they are affected. These represent the false negative cases. A risk cutoff value of 2.0 MOM will result in a higher detection rate, but also a higher false positive rate. Many pregnant women will be told their fetus is at risk for being born with spina bifida, when in fact the fetus may be unaffected. Conversely, a risk cutoff value of 3.0 MOM will result in a lower detection rate and a lower false positive rate. Many pregnant women will be told their fetus is not at risk for being born with spina bifida, when in fact the fetus is at risk. There is no doubt that selecting a risk cutoff value is difficult because of the consequences of selecting higher or lower detection rates.

As stated earlier, the risk cutoff value for detecting cases of spina bifida is not consistent. It varies across areas in the United States and across countries. The ability and method to compare clinical results among different sites was established in the First U.K. Collaborative study. The study determined that the best method to compare results from the various laboratories was to express all MSAFP measurements as multiples of the median (MOM). As a result, the most common cutoff values currently being used are 2.0 and 2.5 MOM (the cutoff point is defined as the MSAFP concentration at or above which additional diagnostic procedures would be implemented). At the 2.5 MOM value, this study showed that 79% of pregnancies with spina bifida were associated with an MSAFP level at or above this cutoff value (Appendix 2). The corresponding false positive rate was 3.3%. The study also looked at 2.0 MOM, which identified 91% of pregnancies with spina bifida. However, it was also noted that this high sensitivity was at the expense of a greater number of screen-positive pregnancies not affected with spina bifida, a larger percentage of false positive results. The false positive rate was 7.2%. At first glance, this may seem low compared to the 91% of affected pregnancies that would test true positive. However, using the current United States figure of 4,064,948 million births per year, this would translate into 263,409 (3,658,453 births x 7.2%) fetuses testing positive for spina bifida, when in fact they are unaffected (assuming that 90% of pregnant women would be screened).

The U.K. Collaborative Study established the most efficient risk cutoff value based on a specific level of false positive cases acceptable to the scientific community. However, this evaluation was not conducted from the perspective of society and disregarded the maximization of net economic benefits. In the current environment of increasing medical costs and managed care cost containment issues, resources clearly have alternative uses. The purpose of this evaluation is to determine the best way of utilizing these resources.

EPIDEMIOLOGY

Three main types of neural tube defects are anencephaly, spina bifida and encephalocele. Anencephaly and spina bifida account for approximately 50% and 45%, respectively, of all neural tube defects. Encephalocele is rare, accounting for the remaining 5%. "Anencephaly is fatal at, or within hours of birth, but the outcome of spina bifida is variable" (Wald and Cuckle, 1984). In unaffected pregnancies, the spine encloses and protects the spinal cord. Spina bifida occurs when the spinal cord does not develop properly and the vertebrae and skin cannot form around it.

There are several types of spina bifida, each varying in severity. The most familiar and most serious type is open spina bifida (also called meningomyelocele). In such cases, the spinal cord does not close properly during the first month of pregnancy, resulting in an open lesion. This type of spina bifida can be life threatening during infancy and causes mild to severe disabilities in those who survive. Often those affected are stillborn or die in infancy, while many of the survivors need surgical intervention, remedial therapy, aids to mobility and special education, and some need institutional care throughout their lives. As stated earlier, disabilities are common in individuals affected with open spina bifida. "Even with the best surgical intervention 25% to 60% (depending on age group being studied) remain wheel-chair bound, between 6% and 40% are reported to have serious mental impairment, up to 85% are severely handicapped and 90% show urinary incontinence" (Furhmann and Weitzel, 1992). Prenatal screening tests and ultrasound examinations during pregnancy are used to detect open spina bifida in a fetus. However, there are cases of spina bifida where the spinal cord does not close properly, but where a thick membrane covers the opening (also called closed spina bifida). These cases of closed spina bifida cannot be detected by screening. Therefore, this paper will only be evaluating those cases of open spina bifida.

The average life expectancy for people born with spina bifida has improved over the years. Today, life expectancy is normal for most children born with this condition. The prognosis is influenced by many factors, including medical status and complications, independence in activities of daily living, and educational training and opportunities.

OBJECTIVES

Cutoff values have been established to define pregnancies at high risk for spina bifida without regard to optimization. This optimal value needs to be established. Screening requires a trade-off between the detection rate and false positive rate. The purpose of this paper is to find the optimal risk cutoff value from the perspective of society. It needs to be stressed that this evaluation does not place a value on an affected individual's life. Affected and unaffected individuals differ only with respect to the social costs associated with medical treatment and lost earnings. Conducting a cost-benefit analysis will identify the optimal cutoff value and level of net benefits to society. This paper will utilize a net benefit formula to illustrate the various levels of net social benefits associated with spina bifida screening.

METHODS

Evaluating the net benefit of prenatal screening for spina bifida will be determined by using United States population and birth statistics and calculating the net benefit from the perspective of society. The unit of measurement for the net benefit will be expressed as a dollar amount. The net benefit formula, originally developed to maximize the net benefit in Down syndrome screening (Beazoglou, et al., 1998), has been modified based on parameters specific to spina bifida. In order to identify the optimal risk cutoff value, various pairs of detection and false positive rates associated with alternative cutoff values will be applied to the net benefit formula. The detection rate is defined as the rate of true positive cases. The unit of measurement for the risk cutoff value will be expressed as a MOM. This formula will identify the combination, and hence the risk cutoff value, that provides the maximum net benefit per case to society. This approach includes a combination of clinical and economic variables of prenatal screening for spina bifida. It is important to note that assumptions were made for selected variables as a result of a lack of existing data. Uptake rates for MSAFP screening, routine ultrasound screening and amniocentesis were assumed (90%, 70%, 70%, respectively) and based on uptake rates for prenatal screening for Down syndrome. The net benefit for the MSAFP screening test is defined as:

$$NB = [I \times D \times U \times F1 \times S(F2 \times (B-C1))] - [C2+C3 \times U(D \times I+FP(1-I))]$$

NB	=	Net benefit per screened individual
I	=	Incidence rate
D	=	Detection rate of MSAFP screening test
U	=	Uptake rate for amniocentesis (after positive screening test)

F1	=	Fetus survival rate following amniocentesis
S	=	Termination rate following positive amniocentesis
F2	=	Fetus survival rate to birth
B	=	Benefits of prenatal screening (cost savings from preventing birth of affected child)
C1	=	Cost of abortion
C2	=	Cost of MSAFP screening test
C3	=	Cost of amniocentesis
FP	=	False positive rate of MSAFP screening test

This formula is made up of two parts: benefits and costs. The difference between the two is the net benefit, measured in dollars. The first half of the formula represents the benefit side:

$$[I \times D \times U \times F1 \times S(F2 \times (B - C1))]$$

The benefits of prenatal screening are defined as preventing the birth of a baby with spina bifida. The incidence rate (I) is defined by the affected and unaffected pregnancies at the time of screening. The detection rate (D) defines the sensitivity of the screening test. The incidence and detection rates are variable in this formula. As previously mentioned, the uptake rate (U) used is based on assumptions. The fetal survival rate (F1) defines the rate of fetuses that survive to birth. The fetal termination rate (S) addresses the rate of abortions after a positive amniocentesis. The fetus survival rate to birth (F2) defines the rate that fetuses make it through the term of pregnancy and factors in human intervention and spontaneous abortion (unrelated to amniocentesis). The benefit of prenatal screening (B) defines the lifetime cost for an individual with spina bifida. This cost includes lifetime direct medical, developmental and special education costs, as well as lifetime lost wages and productivity. The last component of the benefit side of the formula is the cost of having an abortion (C1). This represents the fetuses that do not make it to term due to human intervention. The second half of the formula represents the cost side:

$$[C2+C3 \times U(D \times I+FP(1-I))]$$

The costs are defined as the direct costs per patient associated with prenatal screening. The costs for MSAFP screening (C2) and amniocentesis (C3) are fixed at $20 and $1200, respectively.

The following table shows the above variables with their associated costs and values.

I	=	1:500, 1:1000; 1:1500,1:2000, 1:2500 ,1:3000
D	=	Variable (according to model)
U	=	70% (this can vary and be adjusted as needed)
F1	=	0.995% (Vintzileos, et al., 1998)
S	=	0.90% (assumption based on Beazoglou, et al., 1998)
F2	=	.097 (Beazoglou, et al., 1998)
B	=	$532,000 (MMWR, 1995)
C1	=	$2000 (Vintzileos, et al., 1998)
C2	=	$20 (Beazoglou, et al.,1998)
C3	=	$1200 (Vintzileos, et al.,1998)
FP	=	Variable (according to model)

The three components that drive this formula are the incidence rate, detection rate and false positive rate and each one varies. In an effort to simplify this complicated formula, the specified rates and costs in the above table can be calculated into constant values. The resulting simplified formula is:

$$NB= [322,226 \times I \times D] - [20 + 840(D \times I + FP (1-I))]$$

Once the incidence rate is selected, the corresponding false positive and detection rates are inserted into the formula and multiplied by the corresponding constant values. Another way to illustrate the steps in the formula is with a decision-making tree that can be found in Appendix 3. This shows the progression of steps that a pregnant woman takes with regard to prenatal screening.

The CDC uses 1:2174 for the incidence of spina bifida at birth in the United States. This represents the risk, unadjusted for maternal age, of having a child with spina bifida. Although the incidence rate for spina bifida screening is a main determinant of calculating the varying net benefits per individual, the incidence rate is not uniform across clinics in this country. Therefore, the following incidence rates will be included in the analysis: 1:500, 1:1000; 1:1500,1:2000, 1:2500 and 1:3000. Depending on which incidence rate is selected in each clinic, the maximum net benefit will be determined in this evaluation. It is important to note that the incidence of spina bifida at birth is being used in this evaluation. The true incidence of spina bifida occurring during pregnancy is higher. It is difficult to determine the true incidence during pregnancy because the rate of spontaneous abortion and human intervention directly affects this.

Currently, there is not enough existing data to report on prenatal screening for spina bifida. Some detection and false positive rates have been published (Wald, et al., 1984; Wald, et al., 1992; Haddow and Palomaki, 1992). However, this analysis requires more data than what is currently available. Therefore, this evaluation will utilize a simulation model (Reynolds, et al., 1993) to execute the net benefit formula. This model was developed into a computer program that is based on the statistical software S-Plus (S-PLUS 4, 1997). This simulation program will give the estimated risk of a neural tube defect pregnancy at various detection and false positive rates. It is important to note that the results of the simulation are similar to published data for spina bifida screening. The model will generate risk cutoff values for 100,000 affected and 100,000 unaffected cases based on summary statistics (means and standard deviations). Wald and Cuckle published these parameters in 2000 (Wald and Cuckle, 2000). Once the incidence rates are specified, the program will generate pairs of detection and false positive rates, as well as the corresponding MOM levels and risks. The final step after the simulation is to calculate the net benefit per case. The formula is inserted into an Excel spreadsheet. The only variables in this formula are the three rates that drive the formula: incidence rate, false positive rate and the detection rate. Therefore, the three resulting rates from the simulation are entered into the net benefit formula. The net benefit per case will be automatically calculated.

It has been mentioned in some of the literature that some clinics that provide pregnant women access to genetic ultrasound screening (versus routine ultrasound screening) do not typically recommend amniocentesis. The accuracy for detecting cases of open spina bifida with the genetic ultrasound screening is more than 90%. In order to address the protocol for these selected clinics, the formula will be slightly modified:

$$NB = [I \times D \times U \times S(F2 \times (B-C1))] - [C2+C3 \times U(D \times I+FP(1-I))]$$

Changes to the original formula include the exclusion of the risk of spontaneous abortion (due to amniocentesis) and to the cost of the ultrasound after screening (C3) is \$300. The results will be evaluated and shown for both screening protocols in Appendices 4, 5 and 6.

RESULTS

Several incidence rates were evaluated (1:500, 1:1000, 1:1200, 1:1500,1:2000, 1:2174, 1:2500 and 1:3000) in order to determine the net benefit per case for each pairing of detection and false positive rates. For every incidence rate, the corresponding MOM, risk and net benefit per case (based on amniocentesis or ultrasound screening protocols) will be derived. Appendices 4, 5 and 6 show the results for each incidence rate (assuming a 70%, 80% and 60% amniocentesis uptake rate, respectively) after MSAFP screening.

Several key findings have emerged from this analysis. It appears that for a number of different incidence rates and at different uptake rates, the optimal risk cutoff value may not be unique. Appendix 7 shows a summary of the results at the 1/2174 incidence rate. Based on the simulation, using a rate of 1:360, which is equivalent to 2.8 MOM, the following 69% detection rate and 1% false positive rate are generated. These two values, along with the 1/2174 incidence rate, are inserted into the net benefit formula. The net benefit per case is determined to be $64. Appendix 7 shows that the maximum net benefit per case, at the 1/2174 incidence rate, occurs at this risk rate (or MOM level). These results illustrate that as the detection rate decreases, the false positive rate also decreases, while the net benefit per case increases. This occurs only until the 2.8 MOM level. At that point, the net benefit per case begins decreasing. At the 1/2174 incidence rate (assuming 70% uptake rate), there is one optimal risk cutoff value. However, other incidence rates show multiple optimal risk cutoff values.

The results in Appendix 4 for the incidence rate 1/500 illustrate that the net benefit per case for amniocentesis is \$457. This optimal net benefit occurs at two separate MOMs (2.0 and 2.1) and two different risk values (1/400 and 1/320). Similarly, the ultrasound protocol for the same incidence and uptake rate shows that there are two different optimal risk cutoff values and net benefit amounts. According to the ultrasound protocol, the optimal risk cutoff values are at 1.4 and 1.5 MOMs and have a corresponding net benefit of \$540. Overall, the results obtained at different incidence and uptake rates show that in many cases, two or three risk cutoff values yield the maximum net benefit. The results in Appendix 4, at each specified incidence rate, show that there may be more than one MOM level that achieves the maximum net benefit per case. For an incidence rate of 1/1000, the optimal net benefit per case occurs at 2.3 and 2.4 MOM in the amniocentesis screening protocol. These two levels show the maximum net benefit per case is \$194. The corresponding risk values are 1:430 and 1:350, respectively. These risk values are higher than those at lower MOM levels. If 2.0 MOM is used as the cutoff value, the net benefit per case decreases to \$184, and the risk decreases to 1:810. If the ultrasound protocol is utilized at this incidence rate of 1/1000, the maximum net benefit per case is \$242 at 1.7 MOM.

Another key finding is that a lower incidence rate implies a higher optimal MOM and lower net benefit. Appendix 8 shows a summary of the maximum net benefits across selected incidence rates. As the incidence rate decreases, 1/1000 to 1/2000, the maximum net benefit per case also decreases. The optimal MOM rate, on the other hand, increases. The incidence rate of 1/1000 (according to the amniocentesis screening protocol) shows the maximum net benefit per case at $194. The maximum net benefit per case occurs at 2.3 and 2.4 MOMs. At the incidence rate 1/2000, the maximum net benefit per case decreases to $74 and the MOM rate increases and occurs at 2.6, 2.7 and 2.8. The risk cutoff value remains relatively similar. At the 1/1000 incidence rate, the risk cutoff values at the maximum net benefit ($194) are 1:350, 1:430. At the 1/2500 rate, the risk cutoff values at the maximum net benefit ($52) are 2.8, 2.9, 3.0 MOMs (1:410, 1:350 and 1:290, respectively). These risk cutoff values do not appear to vary greatly among the maximum net benefits per case among incidence rates.

As the amniocentesis and ultrasound protocols slightly vary, the results also vary. Across the selected incidence rates, the maximum net benefits per case are consistently higher in the ultrasound protocol than the amniocentesis. The corresponding MOM levels tend to be lower in the ultrasound protocol as well. At the 1/1000 incidence rate (assuming 70% uptake rate), the maximum net benefit for the amniocentesis protocol ($194) occurs at 2.3 and 2.4 MOMs. The ultrasound protocol shows that, at this incidence rate, the maximum net benefit per case ($242) occurs at 1.7 MOM. Similarly, at the 1/2500 incidence rate, the maximum net benefit ($52) for the amniocentesis protocol occurs at 2.8, 2.9 and 3.0 MOMs. The ultrasound protocol, at this incidence rate, shows that the maximum net benefit per case ($73) occurs at 2.0, 2.1 and 2.2 MOMs. This pattern is consistent across the different incidence and uptake rates.

The results discussed in this section reflect the various incidence rates selected and include assumptions of uptake rates following MSAFP screening. Uptake rates and other components of this net benefit formula can be modified to represent individual clinics appropriately. One factor that appears to vary from the 60% to 80% uptake rate is the maximum net benefit per case. It appears to be significantly higher in the 80% uptake rate. Conversely, the 60% uptake rate illustrates the maximum net benefit per case results are significantly lower.

DISCUSSION

Evaluating the standard 2.0 and 2.5 MOM cutoff values used in clinics across the United States, the research shows that at specific incidence rates, these do not consistently provide the maximum net benefit per case. At the 70% amniocentesis uptake rate, selecting 2.0 MOM as the cutoff value provides the maximum net benefit only at an incidence rate of 1/500 (according to the amniocentesis screening protocol). Selecting 2.0 MOM as the cutoff value for the ultrasound screening protocol finds the maximum net benefit to occur at the incidence rates of 1/1500,1/2000 and 1/2500.

At the 70% uptake rate, selecting 2.5 MOM as the cutoff value provides the maximum net benefit only at incidence rates of 1/1200 and 1/1500 (according to the amniocentesis screening protocol). Selecting 2.5 MOM as the cutoff value according to the ultrasound screening protocol finds that the maximum net benefit never occurs at any of the incidence rates examined.

If clinical protocol is based on adhering to the most recent incidence rate published by the CDC of 1:2174, the maximum net benefit per case ($64) occurs at 2.8 MOM. The detection rate is 69%, the false positive rate is 1.9% and the risk cutoff is 1:360. One important issue to note is the fact that clinical protocol may compete with the economic results of this evaluation. Ultimately, the incidence rate selected inherently determines the detection rate and false positive rate to use, based on the maximum net benefit. Again, this evaluation shows that the maximum net benefit is $64. However, clinical decision-making may determine that a 69% detection rate is not acceptable. An 85% detection rate may be a more preferred or acceptable clinical protocol. If this were the case, this would result in a 12% false positive rate, where the corresponding net benefit per case is $8. Clinical decision-making is an important factor to weigh when discussing maximizing net benefits. Though this evaluation is based on maximizing the net benefits to society, medical decisions and protocols affect the individual patient.

It is important to note that this evaluation looks at the aggregate risk rather than the individual risk. There are a number of factors that are not taken into consideration that will be discussed later in this section (e.g. maternal weight, race and ethnicity, etc.). Because of the variability of individuals, this approach is helpful however individual factors must be taken into consideration.

There is a progression of steps in the screening process for spina bifida. The pregnant mother is responsible for making a decision at each step in the process. For each decision, there are specific outcomes. At each step in the screening process, each individual patient has a choice to continue further screening. However, decisions need to be made as to how far in the screening process each woman will proceed to ensure that she is carrying an unaffected baby. At each step in the process, there is constantly a risk of spontaneous abortion. Another factor that must be kept in mind is that some screening may yield false negative results.

For MSAFP screening, the optimal net benefits are calculated at different levels of varying pairs of detection and false positive rates. Stated earlier in this paper is the notion that this evaluation has been conducted only from the perspective of society. Therefore, all optimal net benefits are from this perspective. If the goal is to optimize the benefits of MSAFP screening, methods have to be adjusted to ensure that the net benefits are maximized. In the United States, the most common risk cut-off values for MSAFP screening are 2.0 and 2.5 MOM, respectively. However, the policy of selecting these two values has not been with regard to optimizing the net benefits of society. This analysis illustrates the importance of weighing the detection and false positive rates in conjunction with the corresponding net benefit. The current clinical policy results in selection of risk cutoff values that do not maximize net benefits. In addition, in some cases the associated risks are high.

Clinical practice could be improved based on the findings of this evaluation. Utilizing the optimal risk cutoff value could lower the number of amniocenteses performed, thereby reducing the number of fetuses lost by spontaneous abortion. If the optimal value is not used, the number of false negatives or false positives increase (depending on risk cutoff value selected). Overall, clinicians and pregnant mothers would benefit from using the optimal rate.

Other factors that affect the outcome and MSAFP screening include maternal weight, multiple pregnancies, repeat MSAFP testing, folic acid and race. MSAFP levels have been found to increase as maternal weight decreases (Knight and Palomaki, 1992). The explanation behind this is that lighter women have less volume of blood; therefore the AFP levels are more concentrated when entering the maternal circulation than in heavier women (Wald and Cuckle, 1982). The solution is to adjust the MSAFP cutoff value for maternal weight. If no adjustments are made, lighter women and fewer heavier women will test positive for open spina bifida. One study that adjusted the cutoff value to the corresponding maternal weight noted a decrease in the false positive rate from 2.8% to 2.0% (Wald and Cuckle, 1982). There was not a significant change in the detection rate. It is also important to note that the percent of women this affects in the screening population is very small.

Multiple pregnancies are also an issue in MSAFP screening. MSAFP levels tend to be higher in multiple pregnancies than in singleton pregnancies, in proportion to the number of fetuses (Knight and Palomaki, 1992). The problem is to determine the most appropriate MSAFP cutoff rate. Knight and Palomaki offer a logical suggestion: to select a cutoff for twins that would yield the same number of false positive results in a singleton pregnancy. For example, if 2.0 MOM were selected as the cutoff rate for singleton pregnancies, selecting 4.0 MOM for twin pregnancies would be the solution. Although this would result in similar false positive rates, it is likely that the detection rate would decrease. Therefore, this method would not be as efficient. There is not much data available regarding MSAFP levels and multiple pregnancies. There is even less information on multiple pregnancies where either one or all of the fetuses are affected with open spina bifida. The U.K. Collaborative Study reported only 8 cases of multiple pregnancies with affected fetuses (Wald and Cuckle, 1984). In this study, 3.5 MOM was used as the cutoff rate for the cases of multiple pregnancies. This resulted in a less than 50% detection rate. Another issue raised in this situation is an ethical one: how can anyone justify terminating the affected and unaffected twin fetuses? Though it may be unlikely that both fetuses are found to be affected, this is still a controversial issue. Furhmann and Weitzel (1985) determine that "there is no reliable way to derive cut-off values for twin pregnancies from the distribution of AFP values in singletons". The implication is that more studies need to be conducted with twin pregnancies and MSAFP screening.

Opinions differ about the value of repeating MSAFP testing. One opinion is that conducting repeat testing for those cases that test positive will reduce the false positive rate, without affecting the detection rate. The idea is that the pregnancy will be classified correctly after the second test (Knight and Palomaki, 1992). Wald and Cuckle believe that "there is no practical value in carrying out a repeat MSAFP test on either the same or a fresh sample taken up to one month later". The explanation for this is that the fluctuations are so small that it does not provide much of a benefit relative to the additional cost.

Numerous studies have demonstrated that women who take a daily multivitamin containing folic acid before becoming pregnant and in the early weeks of pregnancy have a lower risk of having a baby with a neural tube defect, such as spina bifida or anencephaly, than women who do not take multivitamins during this period.

Race has been reported as also influencing the results of MSAFP screening. The prevalence of open neural tube defects differs among white, black and hispanic women. The National Institutes of Health Collaborative and Perinatal Project reported that the prevalence of open NTDs was significantly higher in white women than in any other race (Phillips and Elias, 1992). According to Knight and Palomaki, "black women have MSAFP values that average 10-15% higher than those of white women." The authors go on confirm that prevalence, however, is higher in white women; "in addition to having higher MSAFP values, black women have only about half the birth prevalence of fetal open NTDs as white women".

CONCLUSIONS

In the United States, pregnant women have a choice in participating in prenatal screening. Similarly, each woman has a choice in electing to undergo further tests, such as ultrasound or amniocentesis. The decision to terminate or to continue a pregnancy is also a choice, even in cases where the fetus tests positive for a specific disorder. There are many ethical issues that are involved in discussions of this nature, especially when the process may lead to termination of an unaffected fetus. This analysis is only meant to evaluate prenatal screening from a social and economic perspective. Decisions regarding prenatal testing and outcomes are difficult to make. There are no clear-cut boundaries for "right" or "wrong" decisions. This evaluation simply provides information about the maximum economic net benefit of various protocols. Screening policies should not be based only on an economic perspective, but should also include those of the individual patient.

This paper has evaluated screening for spina bifida by using a net benefit approach. The net benefit approach is a useful tool that addresses a serious problem. Although there is no cure for this birth defect it can be detected and prevented. This analysis uses simulated data, summary statistics and characteristics of the U.S. population and some broad assumptions on the uptake rates for MSAFP screening, ultrasound and amniocentesis. In addition, the paper excludes the effects of maternal age, multiple pregnancies, the effect of folic acid and racial differences. The incidence rate selected ultimately determines the detection and false positive rates. These three components together determine the optimal risk cutoff value that maximizes screening.

RECOMMENDATIONS

The net benefit approach is a useful tool in addressing the issue of screening for open spina bifida. This is an economic perspective and though it should not be ignored, similarly it should not be the only component factored into the decision-making process.

Prenatal screening policies differ across clinics and labs throughout the United States. The research shows that at specific incidence rates, these do not consistently provide the maximum net benefit per case and current screening policies are not being optimized. Therefore, clinics and labs need to use better estimates of incidence rates that reflect the characteristics of the population they are screening. This will affect the welfare of the families and fetuses. For example, if a clinic is using 1:1000 for the incidence rate and assuming a 70% uptake rate, there are two optimal risk cutoff values that should be used: 2.3 and 2.4. For this specific incidence and uptake rate, the net benefit per case is $194.

This research also points to a need for more rigorous studies to evaluate other factors that affect screening that were mentioned in the paper, but not directly included in the analysis. The net benefit method has shown that detection and false-positive rates are directly influenced by the incidence rate selected.

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Appendix 1

Distribution of Screening Values

Figure 1

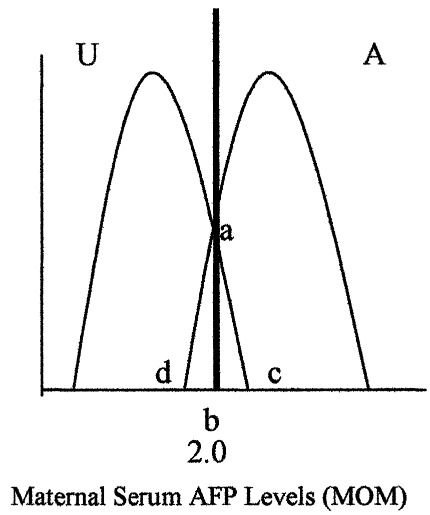
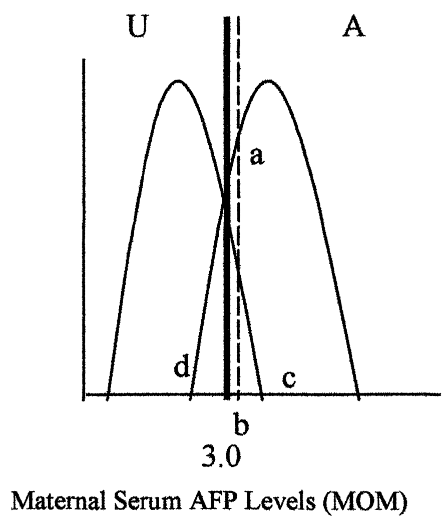


Figure 2



Key:

U= unaffected cases   A= affected cases

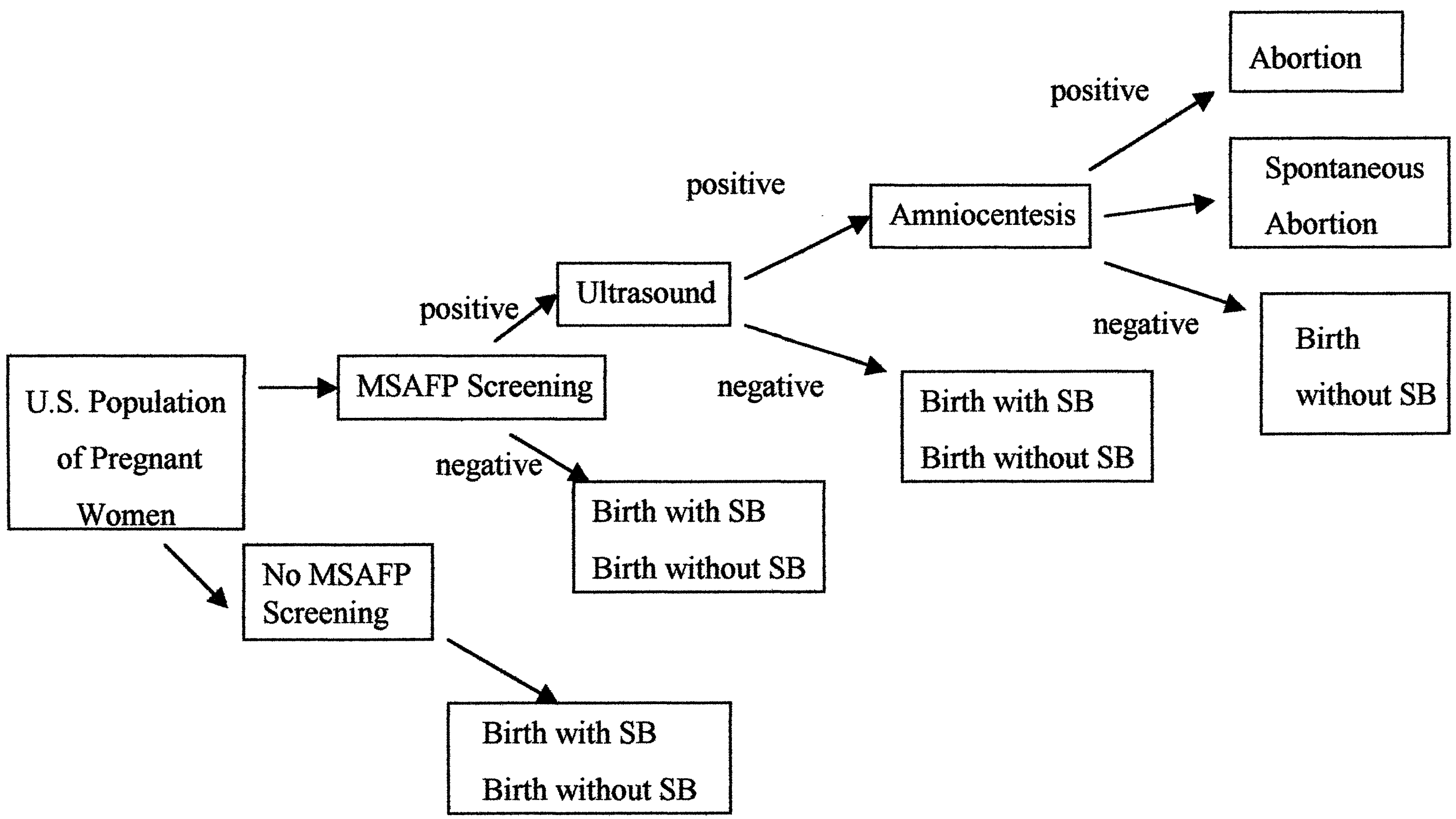
Appendix 2

	Risk Cut-off Rate: percent > or =				
	2.0	2.5	3.0	3.5	4.0
Affected (sensitivity)	91%	79%	70%	64%	45%
Unaffected (false positive rate)	7.2%	3.3%	1.4%	0.6%	0.3%

Table 1 (Detection and false positive rates from the First U.K. Collaborative Study at different risk cutoff rates)

Appendix 3

Decision-Making Tree



Appendix 4

Incidence 1/500			70% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	6300	1	193	512
0.97669	0.42253	4500	1.1	253	523
0.96792	0.35612	3200	1.2	303	532
0.95746	0.29914	2400	1.3	344	537
0.94592	0.24988	1800	1.4	378	540
0.9323	0.2078	1400	1.5	405	540
0.91756	0.17187	1000	1.6	425	538
0.90148	0.14301	820	1.7	439	533
0.88461	0.11906	640	1.8	449	528
0.86732	0.09875	510	1.9	455	521
0.84893	0.08146	400	2	457	512
0.82983	0.06756	320	2.1	457	503
0.80988	0.05648	260	2.2	453	492
0.78956	0.04717	210	2.3	448	481
0.76813	0.03962	170	2.4	440	469
0.74854	0.03305	140	2.5	433	458
0.72785	0.02791	120	2.6	424	445
0.7076	0.02323	99	2.7	415	433
0.68754	0.01977	83	2.8	405	421
0.6665	0.01636	70	2.9	395	408
0.6459	0.01369	59	3	384	395
0.62662	0.01152	50	3.1	373	383
0.60644	0.00977	42	3.2	362	370
0.5877	0.00833	36	3.3	351	359
0.56874	0.00708	31	3.4	340	347
0.55023	0.00594	27	3.5	329	335
0.53238	0.00503	23	3.6	318	324
0.51497	0.00416	20	3.7	308	312
0.49761	0.00355	17	3.8	297	301
0.48094	0.00304	15	3.9	287	291
0.46465	0.0025	13	4	277	280
0.44856	0.00204	11	4.1	267	270
0.43288	0.00181	9.9	4.2	257	260
0.41804	0.00151	8.7	4.3	247	250
0.40434	0.00128	7.7	4.4	239	241
0.39064	0.00109	6.8	4.5	230	233
0.37735	0.00091	6	4.6	222	224
0.36425	0.00076	5.3	4.7	213	216
0.35147	0.00065	4.7	4.8	205	207
0.33945	0.00055	4.2	4.9	198	200
0.32752	0.00048	3.7	5	190	192

Incidence 1/1000			70% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	12500	1	-123	194
0.97669	0.42253	8900	1.1	-61	207
0.96792	0.35612	6500	1.2	-8	218
0.95746	0.29914	4800	1.3	37	227
0.94592	0.24988	3600	1.4	74	234
0.9323	0.2078	2700	1.5	105	238
0.91756	0.17187	2100	1.6	131	241
0.90148	0.14301	1600	1.7	150	242
0.88461	0.11906	1300	1.8	164	241
0.86732	0.09875	1000	1.9	176	240
0.84893	0.08146	810	2	184	238
0.82983	0.06756	650	2.1	190	234
0.80988	0.05648	520	2.2	193	230
0.78956	0.04717	430	2.3	194	226
0.76813	0.03962	350	2.4	194	220
0.74854	0.03305	290	2.5	193	215
0.72785	0.02791	240	2.6	190	210
0.7076	0.02323	200	2.7	188	204
0.68754	0.01977	170	2.8	184	198
0.6665	0.01636	140	2.9	180	192
0.6459	0.01369	120	3	176	186
0.62662	0.01152	100	3.1	172	180
0.60644	0.00977	85	3.2	167	174
0.5877	0.00833	72	3.3	162	168
0.56874	0.00708	62	3.4	157	163
0.55023	0.00594	53	3.5	152	157
0.53238	0.00503	46	3.6	147	151
0.51497	0.00416	40	3.7	142	146
0.49761	0.00355	34	3.8	137	140
0.48094	0.00304	30	3.9	132	135
0.46465	0.0025	26	4	127	130
0.44856	0.00204	23	4.1	122	125
0.43288	0.00181	20	4.2	118	120
0.41804	0.00151	17	4.3	113	115
0.40434	0.00128	15	4.4	109	111
0.39064	0.00109	14	4.5	105	106
0.37735	0.00091	12	4.6	101	102
0.36425	0.00076	11	4.7	96	98
0.35147	0.00065	9.4	4.8	92	94
0.33945	0.00055	8.3	4.9	89	90
0.32752	0.00048	7.4	5	85	86

Incidence 1/1200			70% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	15000	1	-187	130
0.97669	0.42253	10700	1.1	-124	144
0.96792	0.35612	7800	1.2	-70	156
0.95746	0.29914	5800	1.3	-25	165
0.94592	0.24988	4300	1.4	13	172
0.9323	0.2078	3300	1.5	45	178
0.91756	0.17187	2500	1.6	72	181
0.90148	0.14301	2000	1.7	92	183
0.88461	0.11906	1500	1.8	107	184
0.86732	0.09875	1200	1.9	120	184
0.84893	0.08146	970	2	130	183
0.82983	0.06756	780	2.1	137	181
0.80988	0.05648	630	2.2	141	178
0.78956	0.04717	510	2.3	143	175
0.76813	0.03962	420	2.4	144	171
0.74854	0.03305	350	2.5	145	167
0.72785	0.02791	290	2.6	144	163
0.7076	0.02323	240	2.7	142	158
0.68754	0.01977	200	2.8	140	154
0.6665	0.01636	170	2.9	138	149
0.6459	0.01369	140	3	135	144
0.62662	0.01152	120	3.1	131	140
0.60644	0.00977	100	3.2	128	135
0.5877	0.00833	87	3.3	124	130
0.56874	0.00708	74	3.4	120	126
0.55023	0.00594	64	3.5	116	121
0.53238	0.00503	55	3.6	113	117
0.51497	0.00416	48	3.7	109	112
0.49761	0.00355	41	3.8	105	108
0.48094	0.00304	36	3.9	101	104
0.46465	0.0025	31	4	97	100
0.44856	0.00204	27	4.1	94	96
0.43288	0.00181	24	4.2	90	92
0.41804	0.00151	21	4.3	86	88
0.40434	0.00128	18	4.4	83	84
0.39064	0.00109	16	4.5	80	81
0.37735	0.00091	14	4.6	76	78
0.36425	0.00076	13	4.7	73	74
0.35147	0.00065	11	4.8	70	71
0.33945	0.00055	10	4.9	67	68
0.32752	0.00048	8.9	5	64	65

Incidence 1/1500		70% Uptake Rate			
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	18800	1	-228	88
0.97669	0.42253	13400	1.1	-164	103
0.96792	0.35612	9700	1.2	-111	115
0.95746	0.29914	7200	1.3	-65	125
0.94592	0.24988	5400	1.4	-26	133
0.9323	0.2078	4100	1.5	6	139
0.91756	0.17187	3100	1.6	33	143
0.90148	0.14301	2400	1.7	54	145
0.88461	0.11906	1900	1.8	71	147
0.86732	0.09875	1500	1.9	84	147
0.84893	0.08146	1200	2	94	147
0.82983	0.06756	970	2.1	102	146
0.80988	0.05648	790	2.2	107	144
0.78956	0.04717	640	2.3	110	141
0.76813	0.03962	520	2.4	112	138
0.74854	0.03305	430	2.5	113	135
0.72785	0.02791	360	2.6	113	132
0.7076	0.02323	300	2.7	113	129
0.68754	0.01977	250	2.8	111	125
0.6665	0.01636	210	2.9	110	121
0.6459	0.01369	180	3	108	117
0.62662	0.01152	150	3.1	105	113
0.60644	0.00977	130	3.2	102	109
0.5877	0.00833	110	3.3	100	106
0.56874	0.00708	93	3.4	97	102
0.55023	0.00594	80	3.5	93	98
0.53238	0.00503	69	3.6	90	94
0.51497	0.00416	59	3.7	87	91
0.49761	0.00355	51	3.8	84	87
0.48094	0.00304	45	3.9	81	84
0.46465	0.0025	39	4	78	80
0.44856	0.00204	34	4.1	75	77
0.43288	0.00181	30	4.2	72	73
0.41804	0.00151	26	4.3	69	70
0.40434	0.00128	23	4.4	66	67
0.39064	0.00109	20	4.5	63	64
0.37735	0.00091	18	4.6	60	62
0.36425	0.00076	16	4.7	58	59
0.35147	0.00065	14	4.8	55	56
0.33945	0.00055	13	4.9	53	53
0.32752	0.00048	11	5	50	51

Incidence 1/2000		70% Uptake Rate			
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	25000	1	-281	34
0.97669	0.42253	17900	1.1	-218	49
0.96792	0.35612	13000	1.2	-163	62
0.95746	0.29914	9600	1.3	-117	72
0.94592	0.24988	7200	1.4	-78	81
0.9323	0.2078	5500	1.5	-45	87
0.91756	0.17187	4200	1.6	-17	92
0.90148	0.14301	3300	1.7	5	96
0.88461	0.11906	2600	1.8	22	98
0.86732	0.09875	2000	1.9	36	100
0.84893	0.08146	1600	2	48	100
0.82983	0.06756	1300	2.1	57	100
0.80988	0.05648	1000	2.2	63	99
0.78956	0.04717	850	2.3	67	98
0.76813	0.03962	700	2.4	70	96
0.74854	0.03305	580	2.5	73	94
0.72785	0.02791	480	2.6	74	92
0.7076	0.02323	400	2.7	74	90
0.68754	0.01977	330	2.8	74	87
0.6665	0.01636	280	2.9	73	84
0.6459	0.01369	240	3	72	82
0.62662	0.01152	200	3.1	71	79
0.60644	0.00977	170	3.2	69	76
0.5877	0.00833	140	3.3	67	73
0.56874	0.00708	120	3.4	65	71
0.55023	0.00594	110	3.5	63	68
0.53238	0.00503	92	3.6	61	65
0.51497	0.00416	79	3.7	59	62
0.49761	0.00355	69	3.8	57	60
0.48094	0.00304	60	3.9	55	57
0.46465	0.0025	52	4	53	55
0.44856	0.00204	45	4.1	50	52
0.43288	0.00181	40	4.2	48	50
0.41804	0.00151	35	4.3	46	47
0.40434	0.00128	31	4.4	44	45
0.39064	0.00109	27	4.5	42	43
0.37735	0.00091	24	4.6	40	41
0.36425	0.00076	21	4.7	38	39
0.35147	0.00065	19	4.8	36	37
0.33945	0.00055	17	4.9	34	35
0.32752	0.00048	15	5	32	33

Incidence 1/2174			70% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.984	0.5	27200	1	-298	18
0.97669	0.42253	19400	1.1	-234	34
0.96792	0.35612	14100	1.2	-179	46
0.95746	0.29914	10400	1.3	-133	57
0.94592	0.24988	7800	1.4	-93	65
0.932	0.208	5900	1.5	-60	72
0.918	0.173	4600	1.6	-32	77
0.902	0.143	3500	1.7	-10	81
0.885	0.119	2800	1.8	8	84
0.867	0.099	2200	1.9	22	85
0.849	0.082	1800	2	34	86
0.83	0.068	1400	2.1	43	87
0.81	0.057	1100	2.2	49	86
0.79	0.05	930	2.3	52	85
0.77	0.04	760	2.4	58	84
0.749	0.033	620	2.5	61	82
0.729	0.028	520	2.6	62	80
0.708	0.023	430	2.7	63	78
0.688	0.019	360	2.8	64	76
0.667	0.016	300	2.9	63	74
0.647	0.014	260	3	62	71
0.628	0.012	220	3.1	61	69
0.608	0.0097	180	3.2	60	67
0.589	0.0083	160	3.3	58	64
0.57	0.007	130	3.4	57	62
0.55	0.006	120	3.5	55	59
0.534	0.005	100	3.6	53	57
0.516	0.004	86	3.7	51	54
0.499	0.004	75	3.8	49	52
0.482	0.003	65	3.9	47	50
0.466	0.002	57	4	46	47
0.449	0.002	49	4.1	43	45
0.433	0.002	43	4.2	41	43
0.418	0.002	38	4.3	39	41
0.404	0.001	33	4.4	37	39
0.391	0.001	29	4.5	36	37
0.377	0.001	26	4.6	34	35
0.364	0.001	23	4.7	32	33
0.351	0.001	20	4.8	30	31
0.339	0.001	18	4.9	29	29
0.328	0.0006	16	5	27	28

Incidence 1/2500			70% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	31300	1	-313	2
0.97669	0.42253	22300	1.1	-249	18
0.96792	0.35612	16200	1.2	-195	31
0.95746	0.29914	12000	1.3	-148	41
0.94592	0.24988	9000	1.4	-108	50
0.9323	0.2078	6800	1.5	-75	57
0.91756	0.17187	5200	1.6	-46	63
0.90148	0.14301	4100	1.7	-24	67
0.88461	0.11906	3200	1.8	-6	70
0.86732	0.09875	2500	1.9	9	72
0.84893	0.08146	2000	2	21	73
0.82983	0.06756	1600	2.1	30	73
0.80988	0.05648	1300	2.2	37	73
0.78956	0.04717	1100	2.3	42	72
0.76813	0.03962	870	2.4	45	71
0.74854	0.03305	720	2.5	48	70
0.72785	0.02791	600	2.6	50	68
0.7076	0.02323	500	2.7	51	67
0.68754	0.01977	410	2.8	52	65
0.6665	0.01636	350	2.9	52	63
0.6459	0.01369	290	3	52	61
0.62662	0.01152	250	3.1	51	59
0.60644	0.00977	210	3.2	50	56
0.5877	0.00833	180	3.3	49	54
0.56874	0.00708	150	3.4	47	52
0.55023	0.00594	130	3.5	46	50
0.53238	0.00503	110	3.6	44	48
0.51497	0.00416	99	3.7	43	46
0.49761	0.00355	86	3.8	41	44
0.48094	0.00304	75	3.9	39	42
0.46465	0.0025	65	4	38	40
0.44856	0.00204	57	4.1	36	38
0.43288	0.00181	50	4.2	34	36
0.41804	0.00151	44	4.3	32	34
0.40434	0.00128	38	4.4	31	32
0.39064	0.00109	34	4.5	29	30
0.37735	0.00091	30	4.6	28	29
0.36425	0.00076	26	4.7	26	27
0.35147	0.00065	23	4.8	25	25
0.33945	0.00055	21	4.9	23	24
0.32752	0.00048	19	5	22	22

Incidence 1/3000			70% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	37500	1	-345	-29
0.97669	0.42253	26800	1.1	-281	-14
0.96792	0.35612	19500	1.2	-226	-1
0.95746	0.29914	14400	1.3	-179	10
0.94592	0.24988	10800	1.4	-139	19
0.9323	0.2078	8200	1.5	-105	27
0.91756	0.17187	6300	1.6	-76	33
0.90148	0.14301	4900	1.7	-53	38
0.88461	0.11906	3800	1.8	-35	41
0.86732	0.09875	3000	1.9	-19	43
0.84893	0.08146	2400	2	-7	45
0.82983	0.06756	1900	2.1	3	46
0.80988	0.05648	1600	2.2	11	47
0.78956	0.04717	1300	2.3	17	47
0.76813	0.03962	1000	2.4	21	46
0.74854	0.03305	860	2.5	24	46
0.72785	0.02791	710	2.6	27	45
0.7076	0.02323	590	2.7	29	44
0.68754	0.01977	500	2.8	30	43
0.6665	0.01636	420	2.9	31	41
0.6459	0.01369	350	3	31	40
0.62662	0.01152	300	3.1	31	38
0.60644	0.00977	250	3.2	30	37
0.5877	0.00833	220	3.3	30	35
0.56874	0.00708	190	3.4	29	34
0.55023	0.00594	160	3.5	28	32
0.53238	0.00503	140	3.6	27	31
0.51497	0.00416	120	3.7	26	29
0.49761	0.00355	100	3.8	25	28
0.48094	0.00304	90	3.9	24	26
0.46465	0.0025	78	4	23	25
0.44856	0.00204	68	4.1	22	23
0.43288	0.00181	60	4.2	20	22
0.41804	0.00151	52	4.3	19	20
0.40434	0.00128	46	4.4	18	19
0.39064	0.00109	41	4.5	17	18
0.37735	0.00091	36	4.6	16	16
0.36425	0.00076	32	4.7	14	15
0.35147	0.00065	28	4.8	13	14
0.33945	0.00055	25	4.9	12	13
0.32752	0.00048	22	5	11	12

Appendix 5

Incidence 1/500		80% Uptake Rate			
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	6300	1	223	588
0.97669	0.42253	4500	1.1	292	601
0.96792	0.35612	3200	1.2	349	611
0.95746	0.29914	2400	1.3	396	617
0.94592	0.24988	1800	1.4	435	620
0.9323	0.2078	1400	1.5	465	620
0.91756	0.17187	1000	1.6	489	618
0.90148	0.14301	820	1.7	505	613
0.88461	0.11906	640	1.8	516	606
0.86732	0.09875	510	1.9	522	598
0.84893	0.08146	400	2	525	588
0.82983	0.06756	320	2.1	525	578
0.80988	0.05648	260	2.2	521	566
0.78956	0.04717	210	2.3	515	553
0.76813	0.03962	170	2.4	506	539
0.74854	0.03305	140	2.5	498	526
0.72785	0.02791	120	2.6	488	512
0.7076	0.02323	99	2.7	478	498
0.68754	0.01977	83	2.8	466	484
0.6665	0.01636	70	2.9	454	469
0.6459	0.01369	59	3	441	455
0.62662	0.01152	50	3.1	429	441
0.60644	0.00977	42	3.2	416	426
0.5877	0.00833	36	3.3	404	413
0.56874	0.00708	31	3.4	391	399
0.55023	0.00594	27	3.5	378	386
0.53238	0.00503	23	3.6	366	373
0.51497	0.00416	20	3.7	354	360
0.49761	0.00355	17	3.8	342	347
0.48094	0.00304	15	3.9	330	335
0.46465	0.0025	13	4	319	323
0.44856	0.00204	11	4.1	308	311
0.43288	0.00181	9.9	4.2	296	300
0.41804	0.00151	8.7	4.3	286	289
0.40434	0.00128	7.7	4.4	276	279
0.39064	0.00109	6.8	4.5	266	269
0.37735	0.00091	6	4.6	256	259
0.36425	0.00076	5.3	4.7	247	249
0.35147	0.00065	4.7	4.8	238	240
0.33945	0.00055	4.2	4.9	229	231
0.32752	0.00048	3.7	5	220	222

Incidence 1/1000		80% Uptake Rate			
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	12500	1	-138	224
0.97669	0.42253	8900	1.1	-67	240
0.96792	0.35612	6500	1.2	-6	253
0.95746	0.29914	4800	1.3	45	262
0.94592	0.24988	3600	1.4	88	270
0.9323	0.2078	2700	1.5	123	275
0.91756	0.17187	2100	1.6	152	278
0.90148	0.14301	1600	1.7	174	279
0.88461	0.11906	1300	1.8	191	279
0.86732	0.09875	1000	1.9	204	277
0.84893	0.08146	810	2	214	274
0.82983	0.06756	650	2.1	220	271
0.80988	0.05648	520	2.2	223	266
0.78956	0.04717	430	2.3	225	261
0.76813	0.03962	350	2.4	224	255
0.74854	0.03305	290	2.5	223	249
0.72785	0.02791	240	2.6	221	243
0.7076	0.02323	200	2.7	218	236
0.68754	0.01977	170	2.8	214	230
0.6665	0.01636	140	2.9	209	223
0.6459	0.01369	120	3	204	216
0.62662	0.01152	100	3.1	199	209
0.60644	0.00977	85	3.2	193	202
0.5877	0.00833	72	3.3	188	195
0.56874	0.00708	62	3.4	182	189
0.55023	0.00594	53	3.5	176	182
0.53238	0.00503	46	3.6	171	176
0.51497	0.00416	40	3.7	165	169
0.49761	0.00355	34	3.8	159	163
0.48094	0.00304	30	3.9	154	157
0.46465	0.0025	26	4	148	151
0.44856	0.00204	23	4.1	143	145
0.43288	0.00181	20	4.2	137	140
0.41804	0.00151	17	4.3	132	134
0.40434	0.00128	15	4.4	127	129
0.39064	0.00109	14	4.5	122	124
0.37735	0.00091	12	4.6	118	119
0.36425	0.00076	11	4.7	113	115
0.35147	0.00065	9.4	4.8	108	110
0.33945	0.00055	8.3	4.9	104	105
0.32752	0.00048	7.4	5	100	101

Incidence 1/1200			80% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	15000	1	-210	151
0.97669	0.42253	10700	1.1	-138	168
0.96792	0.35612	7800	1.2	-77	181
0.95746	0.29914	5800	1.3	-26	192
0.94592	0.24988	4300	1.4	18	200
0.9323	0.2078	3300	1.5	55	206
0.91756	0.17187	2500	1.6	85	210
0.90148	0.14301	2000	1.7	108	212
0.88461	0.11906	1500	1.8	126	213
0.86732	0.09875	1200	1.9	140	213
0.84893	0.08146	970	2	151	212
0.82983	0.06756	780	2.1	159	209
0.80988	0.05648	630	2.2	164	206
0.78956	0.04717	510	2.3	167	202
0.76813	0.03962	420	2.4	168	198
0.74854	0.03305	350	2.5	168	194
0.72785	0.02791	290	2.6	167	189
0.7076	0.02323	240	2.7	166	184
0.68754	0.01977	200	2.8	163	179
0.6665	0.01636	170	2.9	160	173
0.6459	0.01369	140	3	157	168
0.62662	0.01152	120	3.1	153	163
0.60644	0.00977	100	3.2	149	157
0.5877	0.00833	87	3.3	145	152
0.56874	0.00708	74	3.4	140	147
0.55023	0.00594	64	3.5	136	141
0.53238	0.00503	55	3.6	132	136
0.51497	0.00416	48	3.7	127	131
0.49761	0.00355	41	3.8	123	126
0.48094	0.00304	36	3.9	118	122
0.46465	0.0025	31	4	114	117
0.44856	0.00204	27	4.1	110	112
0.43288	0.00181	24	4.2	105	108
0.41804	0.00151	21	4.3	101	103
0.40434	0.00128	18	4.4	98	99
0.39064	0.00109	16	4.5	94	95
0.37735	0.00091	14	4.6	90	91
0.36425	0.00076	13	4.7	86	88
0.35147	0.00065	11	4.8	83	84
0.33945	0.00055	10	4.9	79	80
0.32752	0.00048	8.9	5	76	77

Incidence 1/1500			80% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	18800	1	-257	104
0.97669	0.42253	13400	1.1	-185	121
0.96792	0.35612	9700	1.2	-124	134
0.95746	0.29914	7200	1.3	-71	146
0.94592	0.24988	5400	1.4	-27	154
0.9323	0.2078	4100	1.5	10	161
0.91756	0.17187	3100	1.6	41	166
0.90148	0.14301	2400	1.7	65	169
0.88461	0.11906	1900	1.8	83	171
0.86732	0.09875	1500	1.9	99	171
0.84893	0.08146	1200	2	111	171
0.82983	0.06756	970	2.1	119	169
0.80988	0.05648	790	2.2	125	167
0.78956	0.04717	640	2.3	129	164
0.76813	0.03962	520	2.4	131	161
0.74854	0.03305	430	2.5	132	158
0.72785	0.02791	360	2.6	132	154
0.7076	0.02323	300	2.7	132	150
0.68754	0.01977	250	2.8	130	146
0.6665	0.01636	210	2.9	128	141
0.6459	0.01369	180	3	126	137
0.62662	0.01152	150	3.1	123	133
0.60644	0.00977	130	3.2	120	128
0.5877	0.00833	110	3.3	117	124
0.56874	0.00708	93	3.4	113	119
0.55023	0.00594	80	3.5	110	115
0.53238	0.00503	69	3.6	106	111
0.51497	0.00416	59	3.7	103	107
0.49761	0.00355	51	3.8	99	102
0.48094	0.00304	45	3.9	95	98
0.46465	0.0025	39	4	92	95
0.44856	0.00204	34	4.1	88	91
0.43288	0.00181	30	4.2	85	87
0.41804	0.00151	26	4.3	81	83
0.40434	0.00128	23	4.4	78	80
0.39064	0.00109	20	4.5	75	77
0.37735	0.00091	18	4.6	72	73
0.36425	0.00076	16	4.7	69	70
0.35147	0.00065	14	4.8	66	67
0.33945	0.00055	13	4.9	63	64
0.32752	0.00048	11	5	60	61

Incidence 1/2000			80% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	25000	1	-319	42
0.97669	0.42253	17900	1.1	-246	59
0.96792	0.35612	13000	1.2	-184	74
0.95746	0.29914	9600	1.3	-131	85
0.94592	0.24988	7200	1.4	-86	95
0.9323	0.2078	5500	1.5	-48	103
0.91756	0.17187	4200	1.6	-16	108
0.90148	0.14301	3300	1.7	8	112
0.88461	0.11906	2600	1.8	28	115
0.86732	0.09875	2000	1.9	45	117
0.84893	0.08146	1600	2	58	117
0.82983	0.06756	1300	2.1	68	117
0.80988	0.05648	1000	2.2	75	116
0.78956	0.04717	850	2.3	80	115
0.76813	0.03962	700	2.4	83	113
0.74854	0.03305	580	2.5	86	111
0.72785	0.02791	480	2.6	87	108
0.7076	0.02323	400	2.7	88	105
0.68754	0.01977	330	2.8	87	102
0.6665	0.01636	280	2.9	87	99
0.6459	0.01369	240	3	85	96
0.62662	0.01152	200	3.1	84	93
0.60644	0.00977	170	3.2	82	90
0.5877	0.00833	140	3.3	80	87
0.56874	0.00708	120	3.4	78	83
0.55023	0.00594	110	3.5	75	80
0.53238	0.00503	92	3.6	73	77
0.51497	0.00416	79	3.7	71	74
0.49761	0.00355	69	3.8	68	71
0.48094	0.00304	60	3.9	65	68
0.46465	0.0025	52	4	63	65
0.44856	0.00204	45	4.1	60	62
0.43288	0.00181	40	4.2	58	60
0.41804	0.00151	35	4.3	55	57
0.40434	0.00128	31	4.4	53	54
0.39064	0.00109	27	4.5	51	52
0.37735	0.00091	24	4.6	48	50
0.36425	0.00076	21	4.7	46	47
0.35147	0.00065	19	4.8	44	45
0.33945	0.00055	17	4.9	42	43
0.32752	0.00048	15	5	40	40

Incidence 1/2174			80% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.984	0.5	27200	1	-337	24
0.97669	0.42253	19400	1.1	-264	41
0.96792	0.35612	14100	1.2	-202	56
0.95746	0.29914	10400	1.3	-149	68
0.94592	0.24988	7800	1.4	-103	77
0.932	0.208	5900	1.5	-66	85
0.918	0.173	4600	1.6	-34	91
0.902	0.143	3500	1.7	-8	96
0.885	0.119	2800	1.8	12	99
0.867	0.099	2200	1.9	28	101
0.849	0.082	1800	2	42	102
0.83	0.068	1400	2.1	52	102
0.81	0.057	1100	2.2	59	101
0.79	0.05	930	2.3	63	99
0.77	0.04	760	2.4	69	99
0.749	0.033	620	2.5	72	97
0.729	0.028	520	2.6	74	95
0.708	0.023	430	2.7	75	92
0.688	0.019	360	2.8	75	90
0.667	0.016	300	2.9	75	87
0.647	0.014	260	3	74	84
0.628	0.012	220	3.1	72	82
0.608	0.0097	180	3.2	71	79
0.589	0.0083	160	3.3	69	76
0.57	0.007	130	3.4	67	73
0.55	0.006	120	3.5	65	70
0.534	0.005	100	3.6	63	68
0.516	0.004	86	3.7	61	65
0.499	0.004	75	3.8	59	62
0.482	0.003	65	3.9	57	60
0.466	0.002	57	4	55	57
0.449	0.002	49	4.1	52	54
0.433	0.002	43	4.2	50	52
0.418	0.002	38	4.3	48	49
0.404	0.001	33	4.4	46	47
0.391	0.001	29	4.5	44	45
0.377	0.001	26	4.6	41	43
0.364	0.001	23	4.7	39	40
0.351	0.001	20	4.8	37	38
0.339	0.001	18	4.9	36	36
0.328	0.0006	16	5	34	34

Incidence 1/2500	80% Uptake Rate				
Detection Rate	**False-Positive**	**Risk 1:/**	**MOM**	**Net Benefit Per Case Amniocentesis**	**Net Benefit Per Case Ultrasound**
0.98388	0.49958	31300	1	-355	6
0.97669	0.42253	22300	1.1	-282	23
0.96792	0.35612	16200	1.2	-220	38
0.95746	0.29914	12000	1.3	-166	50
0.94592	0.24988	9000	1.4	-121	60
0.9323	0.2078	6800	1.5	-82	68
0.91756	0.17187	5200	1.6	-50	75
0.90148	0.14301	4100	1.7	-25	79
0.88461	0.11906	3200	1.8	-4	82
0.86732	0.09875	2500	1.9	13	85
0.84893	0.08146	2000	2	27	86
0.82983	0.06756	1600	2.1	37	87
0.80988	0.05648	1300	2.2	45	86
0.78956	0.04717	1100	2.3	51	85
0.76813	0.03962	870	2.4	55	84
0.74854	0.03305	720	2.5	58	83
0.72785	0.02791	600	2.6	60	81
0.7076	0.02323	500	2.7	62	79
0.68754	0.01977	410	2.8	62	77
0.6665	0.01636	350	2.9	62	75
0.6459	0.01369	290	3	62	72
0.62662	0.01152	250	3.1	61	70
0.60644	0.00977	210	3.2	60	67
0.5877	0.00833	180	3.3	58	65
0.56874	0.00708	150	3.4	57	62
0.55023	0.00594	130	3.5	55	60
0.53238	0.00503	110	3.6	53	58
0.51497	0.00416	99	3.7	52	55
0.49761	0.00355	86	3.8	50	53
0.48094	0.00304	75	3.9	48	50
0.46465	0.0025	65	4	46	48
0.44856	0.00204	57	4.1	44	46
0.43288	0.00181	50	4.2	42	44
0.41804	0.00151	44	4.3	40	41
0.40434	0.00128	38	4.4	38	40
0.39064	0.00109	34	4.5	36	38
0.37735	0.00091	30	4.6	35	36
0.36425	0.00076	26	4.7	33	34
0.35147	0.00065	23	4.8	31	32
0.33945	0.00055	21	4.9	29	30
0.32752	0.00048	19	5	28	28

Incidence 1/3000		80% Uptake Rate			
Detection Rate	**False Positive**	**Risk 1:/**	**MOM**	**Net Benefit Per Case Amniocentesis**	**Net Benefit Per Case Ultrasound**
0.98388	0.49958	37500	1	-391	-31
0.97669	0.42253	26800	1.1	-318	-13
0.96792	0.35612	19500	1.2	-255	2
0.95746	0.29914	14400	1.3	-202	14
0.94592	0.24988	10800	1.4	-156	25
0.9323	0.2078	8200	1.5	-117	34
0.91756	0.17187	6300	1.6	-84	41
0.90148	0.14301	4900	1.7	-58	46
0.88461	0.11906	3800	1.8	-37	50
0.86732	0.09875	3000	1.9	-19	53
0.84893	0.08146	2400	2	-5	55
0.82983	0.06756	1900	2.1	7	56
0.80988	0.05648	1600	2.2	15	56
0.78956	0.04717	1300	2.3	22	56
0.76813	0.03962	1000	2.4	27	56
0.74854	0.03305	860	2.5	31	55
0.72785	0.02791	710	2.6	33	54
0.7076	0.02323	590	2.7	36	53
0.68754	0.01977	500	2.8	37	52
0.6665	0.01636	420	2.9	38	50
0.6459	0.01369	350	3	38	48
0.62662	0.01152	300	3.1	38	47
0.60644	0.00977	250	3.2	37	45
0.5877	0.00833	220	3.3	37	43
0.56874	0.00708	190	3.4	36	41
0.55023	0.00594	160	3.5	35	40
0.53238	0.00503	140	3.6	34	38
0.51497	0.00416	120	3.7	33	36
0.49761	0.00355	100	3.8	31	34
0.48094	0.00304	90	3.9	30	33
0.46465	0.0025	78	4	29	31
0.44856	0.00204	68	4.1	27	29
0.43288	0.00181	60	4.2	26	28
0.41804	0.00151	52	4.3	25	26
0.40434	0.00128	46	4.4	23	25
0.39064	0.00109	41	4.5	22	23
0.37735	0.00091	36	4.6	21	22
0.36425	0.00076	32	4.7	19	20
0.35147	0.00065	28	4.8	18	19
0.33945	0.00055	25	4.9	17	18
0.32752	0.00048	22	5	16	16

Appendix 6

Incidence 1/500		60% Uptake Rate			
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	6300	1	163	436
0.97669	0.42253	4500	1.1	214	446
0.96792	0.35612	3200	1.2	257	453
0.95746	0.29914	2400	1.3	292	457
0.94592	0.24988	1800	1.4	321	460
0.9323	0.2078	1400	1.5	344	460
0.91756	0.17187	1000	1.6	362	458
0.90148	0.14301	820	1.7	374	454
0.88461	0.11906	640	1.8	382	449
0.86732	0.09875	510	1.9	387	443
0.84893	0.08146	400	2	389	436
0.82983	0.06756	320	2.1	389	428
0.80988	0.05648	260	2.2	386	419
0.78956	0.04717	210	2.3	381	410
0.76813	0.03962	170	2.4	375	399
0.74854	0.03305	140	2.5	369	389
0.72785	0.02791	120	2.6	361	379
0.7076	0.02323	99	2.7	353	368
0.68754	0.01977	83	2.8	345	358
0.6665	0.01636	70	2.9	335	347
0.6459	0.01369	59	3	326	336
0.62662	0.01152	50	3.1	317	326
0.60644	0.00977	42	3.2	307	315
0.5877	0.00833	36	3.3	298	305
0.56874	0.00708	31	3.4	288	294
0.55023	0.00594	27	3.5	279	284
0.53238	0.00503	23	3.6	270	274
0.51497	0.00416	20	3.7	261	265
0.49761	0.00355	17	3.8	252	255
0.48094	0.00304	15	3.9	243	246
0.46465	0.0025	13	4	234	237
0.44856	0.00204	11	4.1	226	228
0.43288	0.00181	9.9	4.2	217	220
0.41804	0.00151	8.7	4.3	209	212
0.40434	0.00128	7.7	4.4	202	204
0.39064	0.00109	6.8	4.5	194	197
0.37735	0.00091	6	4.6	187	189
0.36425	0.00076	5.3	4.7	180	182
0.35147	0.00065	4.7	4.8	173	175
0.33945	0.00055	4.2	4.9	167	168
0.32752	0.00048	3.7	5	160	162

Incidence 1/1000		60% Uptake Rate			
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	12500	1	-109	163
0.97669	0.42253	8900	1.1	-55	175
0.96792	0.35612	6500	1.2	-10	184
0.95746	0.29914	4800	1.3	28	192
0.94592	0.24988	3600	1.4	61	197
0.9323	0.2078	2700	1.5	87	201
0.91756	0.17187	2100	1.6	109	204
0.90148	0.14301	1600	1.7	125	204
0.88461	0.11906	1300	1.8	138	204
0.86732	0.09875	1000	1.9	148	203
0.84893	0.08146	810	2	155	201
0.82983	0.06756	650	2.1	160	198
0.80988	0.05648	520	2.2	162	194
0.78956	0.04717	430	2.3	164	191
0.76813	0.03962	350	2.4	163	186
0.74854	0.03305	290	2.5	162	182
0.72785	0.02791	240	2.6	160	177
0.7076	0.02323	200	2.7	158	172
0.68754	0.01977	170	2.8	155	167
0.6665	0.01636	140	2.9	152	162
0.6459	0.01369	120	3	148	157
0.62662	0.01152	100	3.1	144	152
0.60644	0.00977	85	3.2	140	146
0.5877	0.00833	72	3.3	136	142
0.56874	0.00708	62	3.4	132	136
0.55023	0.00594	53	3.5	127	132
0.53238	0.00503	46	3.6	123	127
0.51497	0.00416	40	3.7	119	122
0.49761	0.00355	34	3.8	115	117
0.48094	0.00304	30	3.9	110	113
0.46465	0.0025	26	4	106	108
0.44856	0.00204	23	4.1	102	104
0.43288	0.00181	20	4.2	98	100
0.41804	0.00151	17	4.3	94	96
0.40434	0.00128	15	4.4	90	92
0.39064	0.00109	14	4.5	87	88
0.37735	0.00091	12	4.6	83	85
0.36425	0.00076	11	4.7	80	81
0.35147	0.00065	9.4	4.8	76	77
0.33945	0.00055	8.3	4.9	73	74
0.32752	0.00048	7.4	5	70	71

Incidence 1/1200	60% Uptake Rate				
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	15000	1	-163	108
0.97669	0.42253	10700	1.1	-109	121
0.96792	0.35612	7800	1.2	-63	131
0.95746	0.29914	5800	1.3	-24	139
0.94592	0.24988	4300	1.4	9	145
0.9323	0.2078	3300	1.5	36	150
0.91756	0.17187	2500	1.6	59	153
0.90148	0.14301	2000	1.7	76	154
0.88461	0.11906	1500	1.8	89	155
0.86732	0.09875	1200	1.9	100	155
0.84893	0.08146	970	2	108	154
0.82983	0.06756	780	2.1	114	152
0.80988	0.05648	630	2.2	118	150
0.78956	0.04717	510	2.3	120	147
0.76813	0.03962	420	2.4	121	143
0.74854	0.03305	350	2.5	121	140
0.72785	0.02791	290	2.6	120	137
0.7076	0.02323	240	2.7	119	133
0.68754	0.01977	200	2.8	117	129
0.6665	0.01636	170	2.9	115	125
0.6459	0.01369	140	3	112	121
0.62662	0.01152	120	3.1	110	117
0.60644	0.00977	100	3.2	107	113
0.5877	0.00833	87	3.3	104	109
0.56874	0.00708	74	3.4	100	105
0.55023	0.00594	64	3.5	97	101
0.53238	0.00503	55	3.6	94	97
0.51497	0.00416	48	3.7	90	94
0.49761	0.00355	41	3.8	87	90
0.48094	0.00304	36	3.9	84	86
0.46465	0.0025	31	4	81	83
0.44856	0.00204	27	4.1	77	79
0.43288	0.00181	24	4.2	74	76
0.41804	0.00151	21	4.3	71	73
0.40434	0.00128	18	4.4	68	70
0.39064	0.00109	16	4.5	65	66
0.37735	0.00091	14	4.6	63	64
0.36425	0.00076	13	4.7	60	61
0.35147	0.00065	11	4.8	57	58
0.33945	0.00055	10	4.9	54	55
0.32752	0.00048	8.9	5	52	53

Incidence 1/1500			60% Uptake Rate		
Detection Rate	False-Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	18800	1	-198	73
0.97669	0.42253	13400	1.1	-144	86
0.96792	0.35612	9700	1.2	-98	96
0.95746	0.29914	7200	1.3	-59	104
0.94592	0.24988	5400	1.4	-25	111
0.9323	0.2078	4100	1.5	3	116
0.91756	0.17187	3100	1.6	26	120
0.90148	0.14301	2400	1.7	43	122
0.88461	0.11906	1900	1.8	58	123
0.86732	0.09875	1500	1.9	69	123
0.84893	0.08146	1200	2	78	123
0.82983	0.06756	970	2.1	85	122
0.80988	0.05648	790	2.2	89	120
0.78956	0.04717	640	2.3	92	118
0.76813	0.03962	520	2.4	93	116
0.74854	0.03305	430	2.5	94	113
0.72785	0.02791	360	2.6	94	110
0.7076	0.02323	300	2.7	94	107
0.68754	0.01977	250	2.8	93	104
0.6665	0.01636	210	2.9	91	101
0.6459	0.01369	180	3	89	98
0.62662	0.01152	150	3.1	87	94
0.60644	0.00977	130	3.2	85	91
0.5877	0.00833	110	3.3	82	88
0.56874	0.00708	93	3.4	80	84
0.55023	0.00594	80	3.5	77	81
0.53238	0.00503	69	3.6	75	78
0.51497	0.00416	59	3.7	72	75
0.49761	0.00355	51	3.8	69	72
0.48094	0.00304	45	3.9	67	69
0.46465	0.0025	39	4	64	66
0.44856	0.00204	34	4.1	61	63
0.43288	0.00181	30	4.2	59	60
0.41804	0.00151	26	4.3	56	57
0.40434	0.00128	23	4.4	54	55
0.39064	0.00109	20	4.5	51	52
0.37735	0.00091	18	4.6	49	50
0.36425	0.00076	16	4.7	47	48
0.35147	0.00065	14	4.8	44	45
0.33945	0.00055	13	4.9	42	43
0.32752	0.00048	11	5	40	41

Incidence 1/2000			60% Uptake Rate		
Detection Rate	**False Positive**	**Risk 1:/**	**MOM**	**Net Benefit Per Case Amniocentesis**	**Net Benefit Per Case Ultrasound**
0.98388	0.49958	25000	1	-244	27
0.97669	0.42253	17900	1.1	-190	39
0.96792	0.35612	13000	1.2	-143	50
0.95746	0.29914	9600	1.3	-103	59
0.94592	0.24988	7200	1.4	-70	66
0.9323	0.2078	5500	1.5	-41	72
0.91756	0.17187	4200	1.6	-17	76
0.90148	0.14301	3300	1.7	1	79
0.88461	0.11906	2600	1.8	16	81
0.86732	0.09875	2000	1.9	28	83
0.84893	0.08146	1600	2	38	83
0.82983	0.06756	1300	2.1	46	83
0.80988	0.05648	1000	2.2	51	82
0.78956	0.04717	850	2.3	55	81
0.76813	0.03962	700	2.4	57	79
0.74854	0.03305	580	2.5	59	78
0.72785	0.02791	480	2.6	60	76
0.7076	0.02323	400	2.7	61	74
0.68754	0.01977	330	2.8	60	72
0.6665	0.01636	280	2.9	60	70
0.6459	0.01369	240	3	59	67
0.62662	0.01152	200	3.1	58	65
0.60644	0.00977	170	3.2	56	62
0.5877	0.00833	140	3.3	55	60
0.56874	0.00708	120	3.4	53	58
0.55023	0.00594	110	3.5	52	55
0.53238	0.00503	92	3.6	50	53
0.51497	0.00416	79	3.7	48	51
0.49761	0.00355	69	3.8	46	48
0.48094	0.00304	60	3.9	44	46
0.46465	0.0025	52	4	42	44
0.44856	0.00204	45	4.1	40	42
0.43288	0.00181	40	4.2	38	40
0.41804	0.00151	35	4.3	36	38
0.40434	0.00128	31	4.4	35	36
0.39064	0.00109	27	4.5	33	34
0.37735	0.00091	24	4.6	31	32
0.36425	0.00076	21	4.7	30	30
0.35147	0.00065	19	4.8	28	29
0.33945	0.00055	17	4.9	26	27
0.32752	0.00048	15	5	25	25

Incidence 1/2174		60% Uptake Rate			
Detection Rate	**False Positive**	**Risk 1:/**	**MOM**	**Net Benefit Per Case Amniocentesis**	**Net Benefit Per Case Ultrasound**
0.984	0.5	27200	1	-258	13
0.97669	0.42253	19400	1.1	-203	26
0.96792	0.35612	14100	1.2	-156	37
0.95746	0.29914	10400	1.3	-117	46
0.94592	0.24988	7800	1.4	-83	53
0.932	0.208	5900	1.5	-54	59
0.918	0.173	4600	1.6	-31	63
0.902	0.143	3500	1.7	-11	67
0.885	0.119	2800	1.8	4	69
0.867	0.099	2200	1.9	16	70
0.849	0.082	1800	2	26	71
0.83	0.068	1400	2.1	34	71
0.81	0.057	1100	2.2	39	71
0.79	0.05	930	2.3	42	70
0.77	0.04	760	2.4	47	69
0.749	0.033	620	2.5	49	68
0.729	0.028	520	2.6	50	66
0.708	0.023	430	2.7	51	64
0.688	0.019	360	2.8	52	62
0.667	0.016	300	2.9	51	60
0.647	0.014	260	3	50	58
0.628	0.012	220	3.1	49	56
0.608	0.0097	180	3.2	48	54
0.589	0.0083	160	3.3	47	52
0.57	0.007	130	3.4	46	50
0.55	0.006	120	3.5	44	48
0.534	0.005	100	3.6	43	46
0.516	0.004	86	3.7	41	44
0.499	0.004	75	3.8	39	42
0.482	0.003	65	3.9	38	40
0.466	0.002	57	4	36	38
0.449	0.002	49	4.1	34	36
0.433	0.002	43	4.2	32	34
0.418	0.002	38	4.3	31	32
0.404	0.001	33	4.4	29	30
0.391	0.001	29	4.5	28	29
0.377	0.001	26	4.6	26	27
0.364	0.001	23	4.7	25	25
0.351	0.001	20	4.8	23	24
0.339	0.001	18	4.9	22	22
0.328	0.0006	16	5	20	21

Incidence 1/2500			60% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	31300	1	-271	-1
0.97669	0.42253	22300	1.1	-216	12
0.96792	0.35612	16200	1.2	-170	23
0.95746	0.29914	12000	1.3	-130	32
0.94592	0.24988	9000	1.4	-96	40
0.9323	0.2078	6800	1.5	-67	46
0.91756	0.17187	5200	1.6	-43	51
0.90148	0.14301	4100	1.7	-24	54
0.88461	0.11906	3200	1.8	-8	57
0.86732	0.09875	2500	1.9	4	58
0.84893	0.08146	2000	2	15	60
0.82983	0.06756	1600	2.1	23	60
0.80988	0.05648	1300	2.2	29	60
0.78956	0.04717	1100	2.3	33	59
0.76813	0.03962	870	2.4	36	58
0.74854	0.03305	720	2.5	39	57
0.72785	0.02791	600	2.6	40	56
0.7076	0.02323	500	2.7	41	54
0.68754	0.01977	410	2.8	42	53
0.6665	0.01636	350	2.9	42	51
0.6459	0.01369	290	3	41	49
0.62662	0.01152	250	3.1	41	47
0.60644	0.00977	210	3.2	40	46
0.5877	0.00833	180	3.3	39	44
0.56874	0.00708	150	3.4	38	42
0.55023	0.00594	130	3.5	36	40
0.53238	0.00503	110	3.6	35	38
0.51497	0.00416	99	3.7	34	36
0.49761	0.00355	86	3.8	32	35
0.48094	0.00304	75	3.9	31	33
0.46465	0.0025	65	4	29	31
0.44856	0.00204	57	4.1	28	29
0.43288	0.00181	50	4.2	26	28
0.41804	0.00151	44	4.3	25	26
0.40434	0.00128	38	4.4	24	25
0.39064	0.00109	34	4.5	22	23
0.37735	0.00091	30	4.6	21	22
0.36425	0.00076	26	4.7	20	20
0.35147	0.00065	23	4.8	18	19
0.33945	0.00055	21	4.9	17	18
0.32752	0.00048	19	5	16	16

Incidence 1/3000			60% Uptake Rate		
Detection Rate	False Positive	Risk 1:/	MOM	Net Benefit Per Case Amniocentesis	Net Benefit Per Case Ultrasound
0.98388	0.49958	37500	1	-298	-28
0.97669	0.42253	26800	1.1	-243	-15
0.96792	0.35612	19500	1.2	-196	-4
0.95746	0.29914	14400	1.3	-156	6
0.94592	0.24988	10800	1.4	-122	14
0.9323	0.2078	8200	1.5	-93	20
0.91756	0.17187	6300	1.6	-68	25
0.90148	0.14301	4900	1.7	-48	29
0.88461	0.11906	3800	1.8	-33	32
0.86732	0.09875	3000	1.9	-19	34
0.84893	0.08146	2400	2	-8	36
0.82983	0.06756	1900	2.1	0	37
0.80988	0.05648	1600	2.2	6	37
0.78956	0.04717	1300	2.3	11	37
0.76813	0.03962	1000	2.4	15	37
0.74854	0.03305	860	2.5	18	36
0.72785	0.02791	710	2.6	20	36
0.7076	0.02323	590	2.7	22	35
0.68754	0.01977	500	2.8	23	34
0.6665	0.01636	420	2.9	23	33
0.6459	0.01369	350	3	24	31
0.62662	0.01152	300	3.1	23	30
0.60644	0.00977	250	3.2	23	29
0.5877	0.00833	220	3.3	23	27
0.56874	0.00708	190	3.4	22	26
0.55023	0.00594	160	3.5	21	25
0.53238	0.00503	140	3.6	20	23
0.51497	0.00416	120	3.7	20	22
0.49761	0.00355	100	3.8	19	21
0.48094	0.00304	90	3.9	18	19
0.46465	0.0025	78	4	17	18
0.44856	0.00204	68	4.1	16	17
0.43288	0.00181	60	4.2	14	16
0.41804	0.00151	52	4.3	13	15
0.40434	0.00128	46	4.4	12	13
0.39064	0.00109	41	4.5	11	12
0.37735	0.00091	36	4.6	11	11
0.36425	0.00076	32	4.7	10	10
0.35147	0.00065	28	4.8	9	9
0.33945	0.00055	25	4.9	8	8
0.32752	0.00048	22	5	7	7

Appendix 7

Risk Cutoff Values, DR, FPR and Net Benefits

RISK CUTOFF

Rate 1:/	MOM	DR	FPR	NB Per Case
5900	1.5	93%	21%	-$60
2800	1.8	89%	12%	$8
1800	2.0	85%	8%	$34
930	2.3	79%	5%	$52
620	2.5	75%	3%	$61
360	**2.8**	**69%**	**1%**	**$64**
260	3.0	65%	1%	$62

Based on Incidence Rate 1:2174

Appendix 8

Maximum Net Benefits Across Incidence Rates

Incidence Rate	Risk Cutoff Value	MOM	Maximum NB
1:1000	430	2.3	$194
	350	2.4	$194
1:1500	430	2.5	$113
	360	2.6	$113
	300	2.7	$113
1:2000	480	2.6	$74
	400	2.7	$74
	330	2.8	$74
1:2174	360	2.8	$64
1:2500	410	2.8	$52
	350	2.9	$52
	290	3.0	$52